Folia Cardiologica 2021
vol. 16, no. 6, pages 389–393
DOI: 10.5603/FC.2021.0057

ISSN 2353–7752
e-ISSN 2353–7760

Sodium-glucose co-transporter 2 inhibitors therapy: not only for diabetologists

Terapia inhibitorami kotransportera sodowo-glukozowego 2 — nie tylko dla diabetologów

Maria Sawościan, Małgorzata Lelonek

Department of Noninvasive Cardiology, Medical University of Lodz, Łódź, Poland

Abstract

Recently, sodium-glucose co-transporter 2 inhibitors have made a major breakthrough in the treatment of type 2 diabetes mellitus and heart failure (HF). Dapagliflozin and empagliflozin are advised to decrease risk of HF hospitalization as well as cardiovascular (CV) death in heart failure with reduced ejection fraction. Moreover, dapagliflozin has also been shown to be an effective drug in the chronic kidney disease patients' population, reducing the number of renal events and CV mortality.

And sotagliflozin, which is also an inhibitor of sodium-glucose co-transporter 1, occurred to be a beneficial therapy in patients with diabetes, hospitalised due to HF exacerbation. Subsequently, it also seems to be a drug that could be used in heart failure with preserved ejection fraction, however, more studies are needed to support this conclusion.

Key words: SGLT2 inhibitors, heart failure, chronic kidney disease

Folia Cardiologica 2021; 16, 6: 389–393

Introduction

In recent years, large clinical trials have been conducted to prove the effectiveness of sodium-glucose co-transporter 2 inhibitors (SGLT2i), not only in patients with type 2 diabetes mellitus (T2DM) but also among the chronic heart failure with reduced ejection fraction (HFrEF) population. HF often coexists with T2DM [1]. This fact significantly aggravates patients' prognosis as well as increases the risk of major adverse cardiovascular effects (MACE) and hospitalization for HF [1, 2]. Therefore, glycaemic levels should be monitored periodically to minimize the risk of cardiovascular (CV) events [3]. For this reason, the effects of empagliflozin in patients with T2DM and high CV risk were first investigated [4]. The next step was the obvious question of whether SGLT2i would therefore affect HFrEF patients with or without coexisting T2DM.

This paper aims to summarize the results of the Dapagliflozin And prevention of Adverse outcomes in Heart Failure trial (DAPA-HF), EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction trial (EMPEROR-Reduced), Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) and Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial as well as to indicate the conclusions that can be drawn from them.

Address for correspondence: Professor Małgorzata Lelonek, MD, PhD, FESC, FHFA, Zakład Kardiologii Nieinwazyjnej, Katedra Chorób Wewnętrznych i Kardiologii, Uniwersytet Medyczny w Łodzi, ul. Żeromskiego 113, 90–549 Łódź, Poland, phone +48 42 639 35 71, e-mail: malgorzata.lelonek@umed.lodz.pl

Heart failure with a reduced ejection fraction

The results of both studies are similar, although there are subtle differences [5]. To start with, the EMPEROR-Reduced patients' population was significantly smaller (n = 3,730) compared to the DAPA-HF trial (n = 4,744). EMPEROR-Reduced, as well as DAPA-HF researchers, divided the group of patients depending on left ventricular ejection fraction (LVEF) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level related to the heart rhythm (sinus rhythm vs atrial fibrillation). Subsequently, EMPEROR-Reduced respondents were divided into four clinical groups based on the abovementioned parameters. Consequently, EMPEROR-Reduced patients occurred to have a higher level of NT-proBNP compared to the DAPA-HF population [5–7]. Moreover, the estimated glomerular filtration rate (eGFR) level for inclusion criterion was also lower in EMPEROR-Reduced (20 mL/min/1.73 m^2) than in DAPA-HF (30 mL/min/1.73 m^2) [5].

Regarding the characteristics of the studied populations, it is worth noting that T2DM likewise non-diabetic patients accounted for ~ 50% in each of the studies [8].

When it comes to treatment, it should be noted that the recommended angiotensin receptor-neprilysin inhibitor (ARNi) treatment was almost twice as high in EMPEROR-Reduced than in DAPA-HF as well as a more effective treatment in the field of an implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT) [5, 8].

In the EMPEROR-Reduced trial, primary compound result of death from CV reasons or HF hospitalization for HF happened in 361 among 1,863 patients in the treatment group and in 462 among 1,867 patients in the control group. The rate of primary end-point events was 15.8 per 100 patient-years in the empagliflozin group and 21.0 per 100 patient-years in the placebo group [hazard ratio (HR), 0.75; 95% confidence interval (CI): 0.65–0.86, p < 0.001].

The secondary outcomes were consistent with the results of the primary outcome analysis (total number of hospitalizations for HF) — 388 events in the empagliflozin group and 553 in the placebo group (HR 0.70, 95% CI: 0.58–0.85, p < 0.001). During the double-blind treatment period the eGFR decreased lesser in the empagliflozin group than in the placebo group (–0.55 mL/min/1.73 m^2 per year vs. –2.28 mL/min/1.73 m^2 per year), for a between-group difference of 1.73 mL/min/1.73 m^2 per year (95% CI: 1.10–2.37, p < 0.001) [9].

In the DAPA-HF trial, the primary composite outcome of HF exacerbation or death because of CV causes occurred in 386 of 2,373 patients in the dapagliflozin group compared to 502 of 2,371 patients (21.2%) in the placebo group. The rate of primary end-point events was 11.6 per 100 patient-years in the dapagliflozin group and 15.6 per 100 patient-years in the placebo group (HR 0.74; 95% CI: 0.65–0.85, p < 0.001).

When it comes to secondary composite outcomes, the incidence of worsening of HF or death due to CV causes was lower in the dapagliflozin group — 382 events — than in the placebo group — 495 events (HR 0.75, 95% CI: 0.65–0.85, p < 0.001) [6].

Despite slight differences, the EMPEROR-Reduced and DAPA-HF studies share common conclusions. The Heart Failure Association of the European Society of Cardiology has updated its statement on SGLT2i in the treatment of HF and concluded that the effectiveness of canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin in preventing hospitalization due to HF in patients with T2DM and those who are at high CV risk was proven [10]. A comparison of the abovementioned studies, as well as SOLOIST-WHF, is provided in Table 1.

What do we know so far about sotagliflozin?

While the effects of SGLTi on HFrEF are already known, the question of how these drugs might work on heart failure with preserved ejection fraction (HFpEF) has appeared.

Table 1. Summary of clinical trials of sodium-glucose co-transporter-1 and -2 inhibitors

Parameter	EMPEROR-Reduced	DAPA-HF	SOLOIST-WHF
Number of patients	3730	4744	1222
Median LVEF [%]	27	31	35
Median NT-proBNP [pg/mL]	~1900	1437	1799.7
Median eGFR [mL/min/1.73 m^2]	62	66	49.7
Diabetes [%]	50	42	100
ARNi treatment [%]	19	11	16.8
Primary endpoint [HR (95% CI)]	0.75 (0.65–0.86)	0.74 (0.65–0.85)	0.67 (0.52–0.85)
Secondary endpoint [HR (95% CI)]	0.70 (0.58–0.85)	0.75 (0.65–0.85)	0.64 (0.49–0.83)

LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro B-type natriuretic peptide; eGFR — estimated glomerular filtration rate; ARNi — angiotensin receptor-nephrilysin inhibitor; HR — hazard ratio; CI — confidence interval

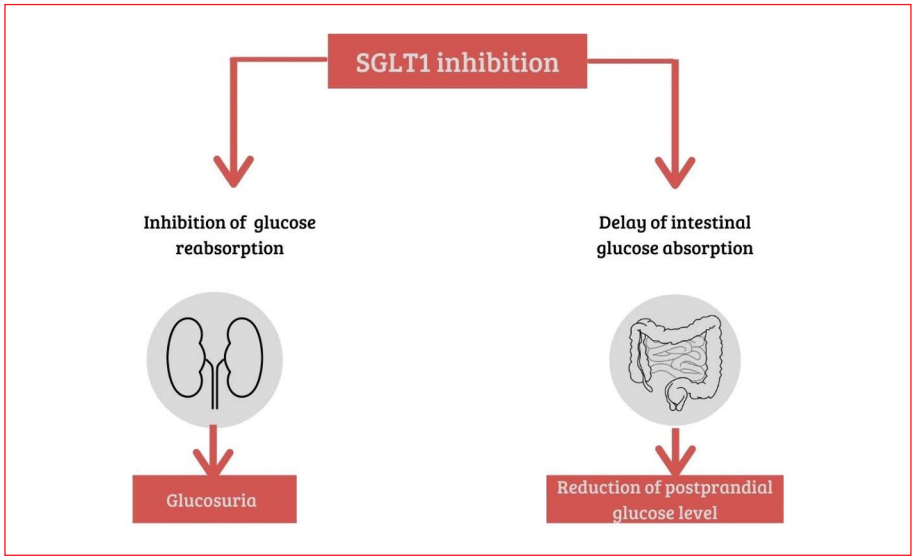

Figure 1. Mechanism of sodium-glucose co-transporter 1 (SGLT1) inhibition

Moreover, the effectiveness of SGLTi after an incident of HF exacerbation remains unknown [11]. The effect of SOLOIST-WHF trial was a consequence of the abovementioned considerations.

Sotagliflozin is not only an SGLT2i, but it also ensures gastrointestinal SGLT1 inhibition, which causes the delay of intestinal glucose absorption that leads to reduction of postprandial glucose level [11].

Patients enrolled in the study were required to have been hospitalized due to worsening of HF with an left ventricular ejection fraction (LVEF) < 50% and ≥ 50% and had been administered intravenous diuretic therapy on hospitalization. Another including criterion required a previous diagnosis of T2DM. The population also needed to have elevated NT-proBNP at the time of randomization. The median glycated haemoglobin level was 7.1%. The patients received adequate therapy for HF, and 85.4% of them were being treated with a glucose-lowering medication. The first intake of sotagliflozin or placebo was administered prior to discharge in 48.8% and a median of 2 days following the discharge in 51.2% [11].

Several 600 primary end-point events happened among 1,222 patients — 245 in the sotagliflozin group and 355 in the placebo group. The rate of primary end-point events was 51.0 per 100 patient-years in the sotagliflozin group and 76.3 per 100 patient-years in the placebo group (HR 0.67; 95% CI: 0.52–0.85, p < 0.001).

The results of the first secondary endpoint analysis (the total number of hospitalizations and urgent visits for HF) were corresponding with the results of the primary end-point analysis — 194 patients in the sotagliflozin group and 297 in the placebo group. The rate of the first secondary endpoint events was 40.4 per 100 patient-years in the sotagliflozin group and 63.9 per 100 patient-years in the placebo group (HR 0.64, 95% CI 0.49–0.83, p < 0.001).

When it comes to the change in the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) score, the difference between those groups was 4.1 points (95% CI: 1.3–7.0) in favour of the sotagliflozin group, and the between-group difference in the change in the eGFR during follow-up was –0.16 mL per minute per 1.73 m^2 (95% CI, –1.30 to 0.98) in favour of the placebo group [11]. Bhatt et al. [11] suggested that SGLT2i with contemporary inhibition of SGLT1 could be beneficial in HFpEF. However, it is too early to draw firm conclusions and more research is needed on a larger patients' HFpEF population than in the SOLOIST-WHF study (n = 256). The mechanism of SGLT1 inhibition is shown in Figure 1.

SGLT2i — not only diabetes and heart failure

Chronic kidney disease (CKD) is another condition where the coexistence of diabetes is very common. Furthermore, this group of patients is at a high risk of adverse renal or CV incidents [12]. Therefore, the DAPA-CKD trial was conducted to assess the influence of dapagliflozin on renal parameters and CV deaths in CKD patients with or without diabetes. The number of 4,304 patients with eGFR of 25 to 75 mL/ /min/1.73 m^2 and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5,000 were randomized to be treated with dapagliflozin (10 mg daily) or with placebo.

The primary outcome event (death from renal or CV causes, a decline of at least 50% in the eGFR or end-stage kidney disease) occurred in 197 of 2,152 participants (9.2%) in the dapagliflozin group and 312 of 2,152 participants (14.5%) in the placebo group (HR 0.61, 95% CI:

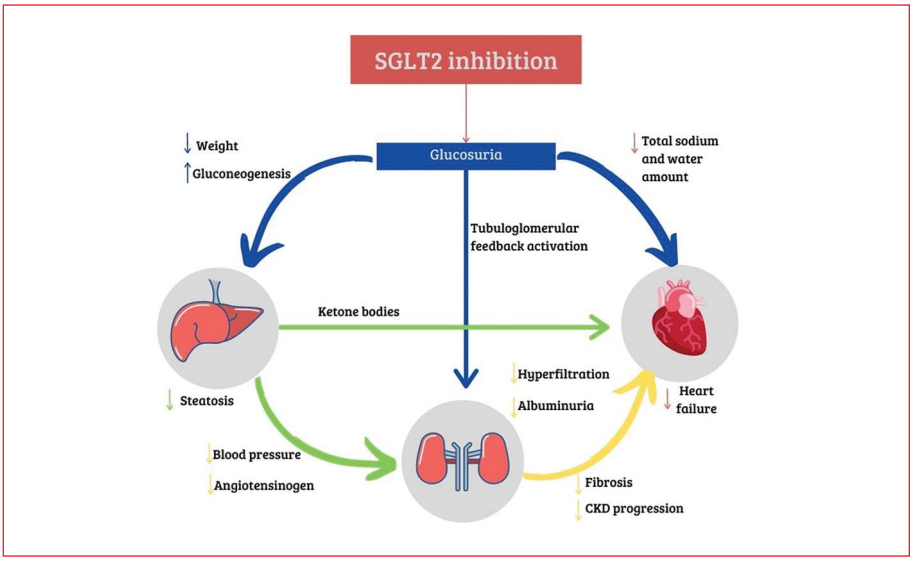

Figure 2. Pleiotropic effect of sodium-glucose co-transporter 2 (SGLT2) inhibitors; CKD — chronic kidney disease

0.51–0.72, p < 0.001). The HR for the composite of a persistent decline in the eGFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI: 0.45–0.68, p < 0.001) [12]. In DAPA-CKD the results of dapagliflozin therapy were similar in participants with T2DM and those without T2DM. The known nephroprotective profile of dapagliflozin was confirmed [12]. Similarly, the nephroprotective effect of dapagliflozin was indicated in the EMPEROR-Reduced study by reducing clinically significant renal events by 50% [13]. The pleiotropic effect of SGLT2i is shown in Figure 2.

Conclusions

Dapagliflozin as well as empagliflozin treatment is recommended to reduce both the risk of HF hospitalization and CV death in symptomatic patients with HFrEF and last but not least — regardless of the presence of the T2DM [12]. Dapagliflozin is also the first nephrologic drug that improves the prognosis for renal and CV endpoints in the CKD patients' population.

Sotagliflozin therapy caused a reduced number of deaths from CV reasons and hospitalizations due to HF acute decompensation in patients with diabetes hospitalized due to worsening HF.

SGLT2i are drugs with multidirectional beneficial effects on the heart, kidneys and diabetes, therefore they are drugs in hands of diabetologists and cardiologists but also for nephrologists.

Conflict of interest

Sawościan M: none; Lelonek M: AstraZeneca, Boehringer Ingelheim — lectures and expert honoraria.

Streszczenie

Ostatnio inhibitory kotransportera sodowo-glukozowego 2 spowodowały, że dokonał się znaczący przełom w leczeniu cukrzycy typu 2 i niewydolności serca (HF). Zaleca się stosowanie dapagliflozyny i empagliflozyny w celu obniżenia ryzyka hospitalizacji z powodu HF i zgonu z przyczyn sercowo-naczyniowych (CV) w niewydolności serca ze zmniejszoną frakcją wyrzutową. Ponadto wykazano, że dapagliflozyna jest skutecznym lekiem w populacji pacjentów z przewlekłą chorobą nerek, zmniejszając liczbę incydentów nerkowych i śmiertelność z przyczyn CV.

Natomiast sotagliflozyna, która jest także inhibitorem kotransportera sodowo-glukozowego 1, okazała się korzystną terapią u chorych na cukrzycę hospitalizowanych z powodu zaostrzenia HF. Co więcej, wydaje się, że jest to lek, który można by stosować w niewydolności serca z zachowaną frakcją wyrzutową, jednak potrzebna jest większa liczba badań, aby potwierdzić ten wniosek.

Słowa kluczowe: inhibitory SGLT-2, niewydolność serca, przewlekła choroba nerek

Folia Cardiologica 2021; 16, 6: 389–393

References

1. Cosentino F, Grant PJ, Aboyans V, et al. ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020; 41(2): 255–323, doi: 10.1093/eurheartj/ehz486, indexed in Pubmed: 31497854.
2. Bies E, Lelonek M. New approach to heart failure in diabetes mellitus. Folia Cardiol. 2019; 14(4): 411–417, doi: 10.5603/fc.a2019.0086.
3. Seferović PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018; 20(5): 853–872, doi: 10.1002/ejhf.1170, indexed in Pubmed: 29520964.
4. Zinman B, Wanner C, Lachin JM, et al. EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373(22): 2117–2128, doi: 10.1056/NEJMoa1504720, indexed in Pubmed: 26378978.
5. McMurray JJV. EMPEROR-Reduced: confirming sodium-glucose co-transporter 2 inhibitors as an essential treatment for patients with heart failure with reduced ejection fraction. Eur J Heart Fail. 2020; 22(11): 1987–1990, doi: 10.1002/ejhf.2006, indexed in Pubmed: 32946169.
6. McMurray JJV, Solomon SD, Inzucchi SE, et al. DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019; 381(21): 1995–2008, doi: 10.1056/NEJMoa1911303, indexed in Pubmed: 31535829.
7. Packer M, Butler J, Filippatos GS, et al. EMPEROR-Reduced Trial Committees and Investigators. Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. Eur J Heart Fail. 2019; 21(10): 1270–1278, doi: 10.1002/ejhf.1536, indexed in Pubmed: 31584231.
8. Verma S, McGuire D, Kosiborod M. Two tales: one story. Circulation. 2020; 142(23): 2201–2204, doi: 10.1161/circulationaha.120.051122.
9. Packer M, Anker SD, Butler J, et al. EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383(15): 1413–1424, doi: 10.1056/NEJMoa2022190, indexed in Pubmed: 32865377.
10. Seferović PM, Fragasso G, Petrie M, et al. Heart Failure Association of the European Society of Cardiology update on sodium-glucose co-transporter 2 inhibitors in heart failure. Eur J Heart Fail. 2020; 22(11): 1984–1986, doi: 10.1002/ejhf.2026, indexed in Pubmed: 33068051.
11. Bhatt DL, Szarek M, Steg PG, et al. SOLOIST-WHF Trial Investigators. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021; 384(2): 117–128, doi: 10.1056/NEJMoa2030183, indexed in Pubmed: 33200892.
12. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020; 383(15): 1436–1446, doi: 10.1056/NEJMoa2024816, indexed in Pubmed: 32970396.
13. Butler J, Zannad F, Filippatos G, et al. Ten lessons from the EMPEROR-Reduced trial. Eur J Heart Fail. 2020; 22(11): 1991–1993, doi: 10.1002/ejhf.2009, indexed in Pubmed: 32949160.